REMARKS/ARGUMENTS

Claims 1-85 are pending in this application. Claims 1-82 have been canceled. Claims 83-85 have been rejected.

Applicants affirm the election of group I (claims 83-85) after a provisional election was made without traverse during a telephone conversation with the Examiner on July 17, 2002. Claims 1-82 have been canceled without prejudice. Applicants retain the right to prosecute claims 1-82 in a divisional application.

Objection Under 35 U.S.C. §132

The amendment filed on August 13, 2001 is objected to under 35 U.S.C. §132 because it allegedly introduces new matter into the disclosure.

The terms "micro-sonicator", "micro-fluidic system", "ultrasonic transmission media", and "ultrasonic excitation of the transmission media" are objected to because these terms allegedly constitute subject matter which was not originally disclosed in the specification. Applicants address this objection below under 35 U.S.C. §112.

Rejection Under 35 U.S.C. §112

Claims 83-85 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The terms "micro-sonicator", "micro-fluidic system", "ultrasonic transmission media", and "ultrasonic excitation of the transmission media" are rejected for allegedly lacking written support in the specification.

The rejection is respectfully traversed.

Applicants direct the Examiner to the following table, wherein support for the above-referenced terms can be found as indicated:

	Support in Provisional Specification:	Support in Subject Specification:
micro-sonicator **sonicated** **sonication**	*page 23, line 1:* ... to shear the nucleic acid during sonication... *page 28, lines 29-32:* As previously described, sample components (e.g., cells spores or organisms in the sample) are captured in the filter stack 87 and lysed by sonication in the lysing chamber 87 to release target analyte (e.g., nucleic acid)... *page 39, lines 22-25:* The lysing chamber 86 is thus pressurized at about 15 psi during sonication since the valve 111 is closed and the lysis chamber is filled with lysing reagent. *page 7, lines 10-13:* Either the instrument or the cartridge may also include processing electronics, e.g., one or more microprocessors, microcontrollers, or memory chips, for controlling the operation of the cartridge. *page 34, lines 28-30:* ...a memory or microprocessor chip may optionally be incorporated as part of the cartridge 20.	*page 64, lines 26-31:* In addition, the lysing chamber 86 may be sonicated (e.g., using an ultrasonic horn coupled to a wall of the chamber) as the sample is forced to flow through the chamber. Sonicating the chamber 86 helps to prevent clogging of the filter stack 87, providing for more uniform flow through the chamber 86. *page 66 and page 67 (lines 1-5):* The transducer 92 is preferably an ultrasonic horn for sonicating the chamber 86. The chamber 86 is preferably sonicated for 10 to 40 seconds at a frequency in the range of 20 to 60 kHz. In the exemplary protocol, the chamber is sonicated for 15 seconds at a frequency of 47 kHz. The amplitude of the horn tip is preferably in the range of 20 to 25 μm (measured peak to peak). *page 28, lines 17-31:* More preferably, the vessel 40 is constructed such that each of the sides walls 57A, 57B, 59A, 59B of the chamber 42 has a length L

	Support in Provisional Specification:	Support in Subject Specification:
	page 104, lines 2-5: In some cases, elongated or spherical interactive regions or chambers may be employed. In general, the interactive regions may vary in dimensions from microscale (microns) to mesoscale (submillimeters) to macroscale (millimeters). *page 42, lines 17-25:* One advantage of the cartridge of the preferred embodiment is that it allows the analyte, e.g. nucleic acid, from a relatively large volume of fluid sample, e.g. several milliliters or more, to be separated from the sample and concentrated into a much smaller volume of reaction fluid, e.g., 100 µl or less. The cartridge of the present invention permits extraordinary concentration factors by efficiently extracting analyte from milliliter quantities of fluid sample.	in the range of 5 to 12 mm, the chamber has a width W in the range of 7 to 17 mm, the chamber has a thickness T in the range of 0.5 to 2 mm, and the ratio of the width W of the chamber to the thickness T of the chamber is at least 4:1. These ranges are more preferable because they provide a vessel having both a larger average optical path length (i.e., 5 to 12 mm) and a volume capacity in the range of 12 to 100 µl while still maintaining a chamber sufficiently thin to permit extremely rapid heating and cooling of a reaction mixture. The relatively large volume capacity provides for increased sensitivity in the detection of low concentration analytes, such as nucleic acids.
micro-fluidic system **fluidic system**	*page 2, line 4:* Anderson et al. disclose such a device for sample processing in an article	*page 9, line 1:* Fig. 40 is a schematic block diagram of a fluidic system incorporating the

	Support in Provisional Specification:	**Support in Subject Specification:**
	entitled "Microfluidic Biochemical Analysis System" (Transducers '97, 1997 International Conference on Solid-State Sensors and Actuators, Chicago, June 16-19, 1997, pg. 477-480).	apparatus of Fig. 36. *page 86, line 24:* Fig. 40 shows a fluidic system for use with the apparatus. *page 46, line 11:* ... and error-free set-up of the instrument 140 for different fluidic processing protocols... *etc.*
ultrasonic transmission media	*page 96, lines 25-29:* Further, although fluorescence excitation and emission detection is a preferred embodiment, optical detection methods such as those used in direct absorption and/or transmission with on-axis geometries may also be applied to the system of the present invention. *page 5, lines 7-11:* The reaction chamber receives the separated analyte (usually in combination with reagents and/or fluorescent dyes for labeling the analyte) and holds the analyte for a chemical reaction (e.g., nucleic acid amplification). *page 6, lines 6-8:* Further, the body of the cartridge preferably	*page 75, lines 12-16:* Further, although fluorescence excitation and emission detection is preferred, optical detection methods such as those used in direct absorption and/or transmission with on-axis geometries may also be used to detect analyte in the cartridge. *page 106, lines 19-24:* If the force is too light, the wall 280A will only be held lightly against the tip 326, leading to poor transmission of the vibratory movement of the transducer 314. If the force is too strong, the container 274 or wall 280A may be damaged during sonication. *page 12 (lines 31-32) and page 13 (lines 1-8):* In particular, the

	Support in Provisional Specification:	**Support in Subject Specification:**
	includes a reagent chamber in fluid communication with the lysing chamber...	middle piece 24 includes a sample chamber 65 for holding a fluid sample introduced through the inlet port 64, a wash chamber 66 for holding a wash solution, a reagent chamber 67 for holding a lysing reagent, a waste chamber 68 for receiving used sample and wash solution, a neutralizer chamber 70 for holding a neutralizer, and a master mix chamber 71 for holding a master mix (e.g., amplification reagents and fluorescent probes) and for mixing the reagents and probes with analyte separated from the fluid sample.
ultrasonic excitation of the transmission media	*page 6, lines 3-13:* A wall of the lysing chamber is preferably formed by a flexible material, and the ultrasonic transducer is coupled directly to the chamber wall. Further, the body of the cartridge preferably includes a reagent chamber in fluid communication with the lysing chamber for holding a lysing reagent and for releasing the lysing reagent into the lysing	*page 18, lines 1-6:* It is presently preferred to use an ultrasonic horn because the horn structure is highly resonant and provides for repeatable and sharp frequency of excitation and large motion of the horn tip. *page 26, lines 13-15:* The side walls 57A, 57B are optically transmissive to permit excitation of the reaction mixture in the chamber 42...

	Support in Provisional Specification:	Support in Subject Specification:
	chamber to contact the captured sample components. The lysing reagent pressurizes the lysing chamber, thereby expanding outwardly the flexible wall of the chamber and ensuring good coupling of the wall to the ultrasonic transducer. *page 9, lines 9-10:* Fig. 26 is a schematic, plan view of an optical excitation assembly of the module of Fig. 24. *page 18, lines 11-12:* The captured components are then lysed in the chamber 86 using ultrasonic energy.	

Applicants respectfully indicate that the specification (including the provisional specification) provides support for "micro-sonicator", "micro-fluidic system", "ultrasonic transmission media", and "ultrasonic excitation of the transmission media" either as explicitly stated or inherently disclosed, as shown in the above table. The skilled artisan would find no difficulty in interpreting the meaning of these terms in light of the specification.

"While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." (see MPEP 2163, subheading *New or Amended Claims*).

Referring to the above table, the specifications teach a micro-sonicator, i.e., a device for sonicating sample components, preferably via an ultrasonic horn. The

subject specification states that the chamber has a length in the range of 5 to 12 mm, a width in the range of 7 to 17 mm, and a thickness in the range of 0.5 to 2 mm; with a volume capacity in the range of 12 to 100 µl which is referred to as a relatively large volume capacity (see table above, specification page 28, lines 17-31). In comparison, the cited art defines a micro-sonicator as one with a container that has a cavity with a depth of 0.025 to 2.0 inch, a width of 0.025 to 2.0 inch, and a length of 0.25 to 2.0 inch (see U.S. Patent No. 6,100,084; column 2, lines 51-53). As such, a 2.0 x 2.0 x 2.0 inch chamber, would hold 131 milliliters of fluid (5.08 x 5.08 x 5.08 cm = 131 cc's = 131 ml) which is much larger than the one described in the subject specification, yet still defined as a micro-sonicator in the art. Hence, it is clear that the subject specification teachings implicitly include a micro-sonicator. In addition, the provisional specification refers to an instrument that may include one or more microprocessors, microcontrollers, and memory or microprocessor chips (see table above, specification page 7, lines 10-13; and page 34, lines 28-30). The provisional specification further refers to interactive regions or chambers that range from microscale (microns) to mesoscale (submillimeters) to macroscale (millimeters); and a relatively large volume of fluid sample, e.g., several milliliters, being concentrated into a much smaller volume of reaction fluid, e.g., 100 µl or less (see table above; specification page 104, lines 2-5; and page 42, lines 17-25). Thus, the provisional specification provides support for a micro-sonicator.

Applicants teach a micro-fluidic system which is explicitly stated in the provisional specification and disclosed in Figure 40 of the subject application.

The specification discloses an ultrasonic transmission media, i.e., transmission of the vibratory movement of the ultrasonic transducer, wherein the sample may be mixed with reagents (or a fluid sample may be used) and the reagent chamber is in fluid communication with the lysing chamber. Since there is ultrasonic transmission of reagents or fluids, wherein reagents and fluids are interchangeable with media, the term media is inherently disclosed. The provisional specification provides support for this disclosure.

Applicants' specification also teaches ultrasonic excitation of the transmission media, i.e., the ultrasonic horn provides for a sharp frequency of excitation and the reaction mixture in the chamber is excited. Thus, the ultrasonic excitation of the

transmission media is inherent within Applicants' disclosure. The provisional specification provides support for this disclosure.

Recent case law indicates that the failure of a specification to specifically mention a limitation that later appears in the claims is not fatal if the skilled artisan would recognize, upon reading the specification, that the new language reflects what the specification shows has been invented. In *All Dental Prodx LLC v. Advantage Dental Products Inc.,* the Federal Circuit reversed the decision of the district court in granting summary judgment that patent claims fail to satisfy the requirements of 35 U.S.C. §112:

"The application for the '498 patent as originally filed did not contain the phrase "original unidentified mass"; indeed, there is not mention of the starting material's shape or form anywhere in the patent specification. However, the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented. *See Eiselstein*, 52 F.3d at 1039, 34 USPQ2d at 1470." (*All Dental Prodx LLC v. Advantage Dental Products Inc.,* 64 USPQ2d 1945 (CA FC 2002).

In light of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 83-85 under 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §102

Claims 83-85 are rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,100,084 (Miles et al.).

The Examiner states that claims 83-85 are not supported by disclosure within the provisional document; that the provisional document is directed away from a micro-sonicator; that there is no disclosure within the provisional document of ultrasonic excitation, ultrasonic transmission media, or ultrasonic waves; and that the provisional document does not disclose a membrane, rather specifies a gasket. Furthermore, the Examiner states that the priority of claims 83-85 is the filing date of the instant application which qualifies U.S. Patent 6,100,084 as prior art.

The rejection is respectfully traversed.

Applicants have addressed the issue of support for specific terms in the specification under section 35 U.S.C. §112 (above) and refer the Examiner to that section.

With respect to the suggestion that Applicants teach away from a micro-sonicator, the Examiner is referred to page 97, lines 11-15 of the provisional, where the specification states that the invention provides "a method and device for the rapid lysing of sample components, e.g., cells, spores, or microorganisms, using ultrasound and a filter stack that includes beads". On page 3, lines 1-6, the specification states that "Of special interest is the detection of low copy concentrations of analytes such as nucleic acid, in which case large sample volumes are required. For example, the minimum theoretically detectable concentration for DNA probe assays necessitates large sample sizes, such as about 10^{-4} liters or more." Hence, the term "large sample sizes/volumes" must be read in light of the specification, wherein it still refers to a relatively small sample size/volume of as little as 0.0001 L. Notwithstanding this example, even the use of larger sample sizes/volumes does not preclude the use of a micro-sonicator. As was indicated above under section 35 U.S.C. §112, U.S. Patent No. 6,100,084 defines a micro-sonicator as one with a container that has a cavity with a depth of 0.025 to 2.0 inch, a width of 0.025 to 2.0 inch, and a length of 0.25 to 2.0 inch (see '084; column 2, lines 51-53). As such, a 2.0 x 2.0 x 2.0 inch chamber, would hold 131 milliliters of fluid (5.08 x 5.08 x 5.08 cm = 131 cc's = 131 ml) which is much larger than the one described in the subject specification, yet still defined as a micro-sonicator. In comparison, the subject specification states that the chamber has a length in the range of 5 to 12 mm, a width in the range of 7 to 17 mm, and a thickness in the range of 0.5 to 2 mm; with a volume capacity in the range of 12 to 100 µl which is referred to as a relatively large volume capacity (see table above, specification page 28, lines 17-31). Clearly, Applicants teach a micro-sonicator that is smaller than the one taught by U.S. Patent No. '084.

With respect to the suggestion that Applicants do not disclose a membrane and rather specify a gasket, the Examiner is referred to page 5, lines 13-15 of the provisional, where the specification states that "In general, the solid support for capturing

the sample components may comprise a filter or membrane, beads, fibers, glass wool, filter paper, polymers or gels."

As shown above (see table), Applicants' disclosure of the subject specification is supported by the provisional application as filed, and Applicants' priority extends back to May 28, 1999 (i.e., filing date of the provisional application). Applicants have also attached a declaration which establishes that the invention date of the instant application predates the filing date of U.S. Patent 6,100,084. Thus, U.S. Patent 6,100,084 (filed on November 5, 1998) does not qualify as an anticipating reference under 35 U.S.C. §102(e) and Applicants respectfully request withdrawal of the rejection of claims 83-85 under 35 U.S.C. §102(e).

Double Patenting

Claims 83-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 1-20 of copending Application No. **09/970,434** in view of U.S. Patent No. 5,856,174 and U.S. Patent No. 6,431,476 B1 (Taylor et al.).

Claims 84 and 85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1 and 2 of copending Application No. **10/006,848** in view of U.S. Patent No. 5,856,174.

Claims 84 and 85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 3 of copending Application No. **10/006,850** in view of U.S. Patent No. 5,856,174.

Claims 83-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-4 of copending Application No. **10/006,904** in view of U.S. Patent No. 5,856,174 and U.S. Patent No. 6,431,476B1 (Taylor et al.).

The rejections are respectfully traversed.

Applicants request that the Examiner withdraw the provisional rejections in accordance with MPEP 804 and allow the earlier filed (May 28, 1999) subject application to issue as a patent. Application No. **09/970,434** is currently pending and was

filed on October 2, 2001. Application Nos. **10/006,848; 10/006,850;** and **10/006,904** are all currently pending and were all filed on November 7, 2001.

MPEP 804 (subsection I, B) states (emphasis added):

"The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. **If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent,** thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

Claims 83-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-73 of U.S. Patent No. 6,440,725 B1 in view of U.S. Patent No. 5,856,174 (Lipshutz et al.).

Applicants hereby file a terminal disclaimer as required by 37 C.F.R. §1.321 over U.S. Patent No. 6,440,725 B1 (U.S. Patent '725). U.S. Patent '725 and the subject application are commonly owned. U.S. Patent '725 was filed on June 25, 1999.

Claims 84 and 85 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 13, 14 and 19 of U.S. Patent No. 6,391,541 B1 (Petersen et al.) in view of U.S. Patent No. 5,856,174.

Applicants hereby file a terminal disclaimer as required by 37 C.F.R. §1.321 over U.S. Patent No. 6,391,541 B1 (U.S. Patent '541). U.S. Patent '541 and the subject application are commonly owned. U.S. Patent '541 was filed on May 30, 2000.

Claims 83-85 are rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-41 of U.S. Patent No. 6,431,476 B1 in view of U.S. Patent No. 5,856,174.

Applicants hereby file a terminal disclaimer as required by 37 C.F.R. §1.321 over U.S. Patent No. 6,431,476 B1 (U.S. Patent '476). U.S. Patent '476 and the subject application are commonly owned. U.S. Patent '476 was filed on December 21, 1999.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

William Schmonsees
Reg. No. 31,796

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PA 3300454 v1

PATENT
Attorney Docket No.: 020048-003120US

#13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: David A. Redding
Taylor, et al.	Art Unit: 1744
Application No.: 09/584,327	DELCARATION OF WILLIAM MCMILLAN UNDER 37 C.F.R. § 1.131
Filed: May 30, 2000	
For: APPARATUS AND METHOD FOR CELL DISRUPTION	

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, William McMillan, depose and say that:

1. I am a joint inventor in the above-identified application.

2. The invention of the above application was conceived in the United States prior to November 5, 1998.

3. I recorded notes in a laboratory book regarding the invention of the above application prior to November 5, 1998. A copy of these laboratory notes is attached hereto as Exhibit A.

4. During the period from a time prior to November 5, 1998, until May 28, 1999, when this application was filed, I was developing and testing prototype models of the invention.

5. My development work as well as the work of others on the invention of this application was continuous from a time well before November 5, 1998 to May 28, 1999 and all of this development work was performed by me and others in the United States.

6. All references to dates prior to November 5, 1998 have been redacted from the exhibits attached hereto.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issued thereon.

Signature: _____

Name: William McMillan

Date: April 25, 2003

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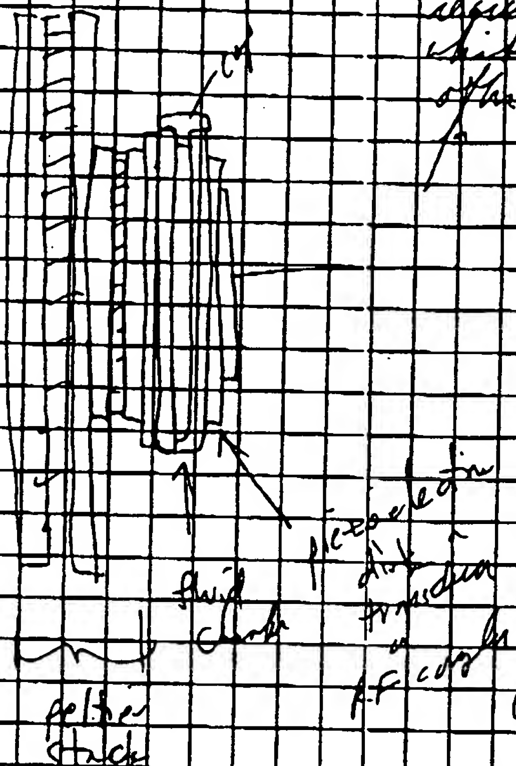
Lysis of Spores: New Concept for Physical Disruption

Purpose: Physical disruption of spores w/o requiring chemical alteration which might inhibit PCR or other enzyme-based detection chemistries for molecular diagnoses.



(1) Per Dr. Kovacs, efficient lysing was considered to be brought about by thermoelectric stacks applied to both sides of a thin wall to achieve efficient freeze-thaw [illegible]

(2) Studies (EXDEC [illegible]) have shown the need to expose Bacillus sp. spores to 1% SDS @ 95°C for 10 minutes and then freeze-thaw in presence of guanidine and/or mercaptoethanol. All these chemicals will inhibit PCR reactions.

New concept is composed of a heating/cooling surface on one side of fluid chamber and is coupled to a piezoelectric energy source or RF source. The water is frozen rapidly down to the range of -10°C to -7°C by the thermoelectric stack. The fluid is held frozen, then the piezoelectric disk is energized and tuned to a frequency that causes the fracturing of the ice sheet. The geometry of the fracturing is predicted to be dependent on the frequency of the energy applied. The fracturing of spores is then effected by disruption by shards of ice, combined with heat or freezing

Read and Understood by [illegible]